The metabolic syndrome as an endocrine disease: is there an effective pharmacotherapeutic strategy optimally targeting the pathogenesis?

Christoph Schindler, MD

Abstract: The metabolic syndrome (MetS) represents a combination of cardiovascular risk determinants such as obesity, insulin resistance and lipid abnormalities such as hypertriglyceridemia, increased free fatty acids, low high-density-cholesterol and hypertension. As a multiple component condition it imparts a doubling of relative risk for atherosclerotic cardiovascular disease (ASCVD). It is currently controversial which component of the syndrome carries what weight. There is even a considerable debate whether the risk for ASCVD is greater in patients diagnosed with MetS than that by the individual risk factors. At present, no unifying pathogenetic mechanism can explain the metabolic syndrome and there is no unique treatment for it. This review summarizes and critically reviews the currently available clinical and scientific evidence for the concept that the MetS is causally an endocrine disease and discusses pharmacotherapeutic strategies targeting the pathogenesis rather than single symptoms of the cluster.

Keywords: Metabolic syndrome, obesity, hypertension, insulin resistance, pharmacotherapy.

Introduction

The metabolic syndrome (MetS) represents a combination of cardiovascular risk determinants such as obesity, insulin resistance, hypertension and lipid abnormalities, for example, hypertriglyceridemia, increased free fatty acids, low high-density-cholesterol and increased low density lipoprotein. In 1988, Reaven first introduced the concept that insulin resistance clusters with glucose intolerance, dyslipidemia, and hypertension to increase cardiovascular risk [Reaven, 1988]. These abnormalities were related to insulin resistance (IR) by cause-effect relationships and it was emphasized that IR alone is insufficient to alter glucose tolerance. IR and hyperinsulinemia are neither strictly necessary nor sufficient to alter lipid metabolism, blood pressure, or vascular function. Each of these systems is under multifactorial control, and defects in one or more steps of its effector pathway are necessary to drive the system out of balance [Ferrannini, 2007]. In the 1990s, the so-called insulin resistance syndrome transmuted into the clinical metabolic syndrome (MetS), which has now taken hold in the medical literature. It has been defined and institutionalized, principally by the World Health Organization (WHO) [Organization WH, 1999] and the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III) [Executive Summary of the NCEP, 2001; Grundy *et al.* 2004], albeit with different definitions. Other organizations have developed similar, but divergent definitions [Balkau *et al.* 2002; Einhorn *et al.* 2003]. As a multiple component condition, the MetS imparts a doubling of relative risk for atherosclerotic cardiovascular disease (ASCVD) [Grundy *et al.* 2005] but it is currently not clear which component of the syndrome carries what weight. However, the fact that the MetS has its own ICD-code suggests that its definition is well sophisticated [Grundy *et al.* 2004; Wilson and Grundy, 2003]. Indeed, there is an ongoing controversial debate among experts about the clinical or pedagogic utility and necessity of creating a diagnostic category of the metabolic syndrome [Ferrannini, 2007; Reaven, 2006]. Critics denounce that its definitions vary,

Correspondence to:
Christoph Schindler, MD
Institute of Clinical
Pharmacology, Medical
Faculty, Technical
University of Dresden,
Fiedlerstrasse 27,
01307 Dresden, Germany
**christoph.schindler@
tu-dresden.de**

it lacks a unifying mechanism [Kahn, 2005], and there is little value in labelling this cluster of obesity, insulin resistance, dyslipidemia, and hypertension as a syndrome. However, independent of its pathogenesis, the majority of experts believes that the MetS is a useful construct in managing cardiovascular disease risk [Third Report of the NCEP, 2002; Alberti *et al.* 2005; Alberti and Zimmet, 1998; Balkau and Charles, 1999; Bestermann *et al.* 2005; Einhorn *et al.* 2003; Grundy *et al.* 2005; Hanefeld *et al.* 2007; Houston *et al.* 2005; Kasper *et al.* 2006; Stolar, 2007]. At present, no unifying pathogenic mechanism is identified and could explain the MetS and hence there is no unique treatment for it.

This review summarizes and critically reviews the currently available clinical and scientific evidence for the concept that the MetS is causally an endocrine disease which is determined by a so far unknown metabolic susceptibility factor determining the risk for clinically developing a MetS. Pharmacologic therapy targeting the different clinical manifestations contributing to the MetS as a cluster will be reviewed with respect to the hypothesis that specific drugs targeting the assumed endocrine pathogenesis might more efficiently treat the cluster of cardiometabolic symptoms rather than one or the other of its components.

Epidemiology of the MetS

Reviewing the literature for studies investigating the epidemiology of the MetS reveals limited and conflicting data. A study performed by Lorenzo *et al.* [2005] surprisingly did not find a significant correlation between increasing central obesity and the effect of the MetS on the risk of coronary heart disease. This might be related to the fact that obesity is not necessarily associated with the MetS in the absence of the presumed but so far unknown metabolic susceptibility factor predisposing for a pathologic metabolic status. However, the majority of epidemiologic studies reports a coherence between visceral obesity and the prevalence of the MetS predicting an increased cardiovascular morbidity [Hubert *et al.* 1983; Urbina *et al.* 1999]. A study performed by Ford *et al.* [2004] reported increased prevalence of the MetS among US adults between 1988 and 1994 and concluded that future increases in diabetes and cardiovascular disease are very likely. The latest epidemiologic data investigating the prevalence of the MetS are published

by Mancia who performed a longitudinal observation cohort study of cardiovascular risk factors in a northern Italian population aged 25 to 74 years [Mancia *et al.* 2007]. The main objective of this study was to assess the relationship between MetS and early death during 12 years of follow-up. The authors report an adjusted risk of cardiovascular and all-cause mortality which was significantly greater in metabolic syndrome subjects (+71.0% and +37.0%; $p < 0.05$), and a further marked increase was observed in patients with left ventricular hypertrophy or blood pressure elevations. The increased risk was related to the blood pressure and the blood glucose component of the MetS, without contribution of the remaining components. The authors concluded that the MetS is common in a Mediterranean population in which it significantly increases the long-term risk of death. Cardiac abnormalities and increases in home and 24-hour blood pressure were also common in the MetS, and their occurrence further enhanced the risk. The MetS was a significant predictor of early death and the two components that apparently explained the association between MetS and mortality were primarily hyperglycemia and high blood pressure. These results suggest that at least in populations of central European descent, these are the two main relevant risk factors on which we should focus for the prevention and deferment of cardiovascular related death.

In the United States, the current increasing annual prevalence of the MetS is driven by the epidemic of obesity occurring throughout the Western World and especially in the Southeastern United States [Houston *et al.* 2005]. In the US, the MetS with the simultaneous expression of excess body weight, insulin resistance, glucose intolerance or type 2 diabetes mellitus, hypertension, dyslipidemia, homocysteinemia, vascular inflammation, and prothrombosis has reached an epidemic level, not only in the southeast but throughout the country. Weiss and colleagues reported that the prevalence of the metabolic syndrome increased with the severity of obesity, and reached a proportion of 50% in severely obese youngsters. The prevalence of the MetS increased significantly with increasing insulin resistance after adjustment for the factors ethnic group and degree of obesity [Weiss *et al.* 2004].

Type 2 diabetes and the MetS have been regarded as a disease of adults for a long time [Zimmet *et al.* 2001] but it has clearly become evident that

the disease can begin at different ages in all ethnic groups and can be already present in childhood [Sinha *et al.* 2002; Sung *et al.* 2003; Wei *et al.* 2003; Weiss *et al.* 2004]. This observation also points towards the existence of a metabolic endocrine susceptibility factor determining the risk for clinically developing a MetS already during childhood. An aggressive global approach to screening and to the management of the metabolic syndrome is therefore recommended to slow the growth of the syndrome throughout the United States [Besterman *et al.* 2005]. Further research should especially focus on the identification of the supposed endocrine master switch determining the metabolic susceptibility.

The issue of pathogenesis of the MetS

Although varying definitions of the MetS exist, all of the commonly used definitions include a measure of obesity, hyperglycemia, hypertension, and dyslipidemia [Executive Summary of the NCEP, 2001; Alberti *et al.* 2006; Alwan and King, 1999]. These definitions are based on expert opinion and not on evidence resulting from prospective epidemiologic studies. Therefore it remains unclear whether single component features of the MetS or the thresholds at which each component is defined as present or absent are informative and optimal for predicting the risk of cardiovascular disease or early death [Franks and Olsson, 2007]. The existence of different definitions actually reflects the uncertainty about the pathogenesis of the MetS. The current understanding of the pathogenesis of the MetS suggests that multiple factors predispose to metabolic susceptibility, for instance genetic defects in insulin signalling pathways, various disorders of adipose tissue, physical inactivity, mitochondrial dysfunction, polygenic variability in individuals and certain ethnic groups, advancing age and certain drugs [Grundy *et al.* 2005]. However, the critical question with respect to the pathogenesis and the several components contributing to the clinical manifestation of the MetS is what came first, the chicken or the egg? In other words, what is the origin of the MetS and which components of the syndrome are more subsequent consequences leading to increased cardiovascular mortality? There is no clear answer yet.

The Framingham study established an increased incidence of cardiovascular events with increasing weight in men and women [Hubert *et al.* 1983]. Body weight and mortality were directly related in the Harvard Alumni Health Study [Lee *et al.* 1993], and weight gain was a significant risk factor for development of diabetes mellitus in women [Colditz *et al.* 1995]. It is also important to emphasize that the association of obesity and increased cardiovascular mortality is not only related to the degree of obesity, but also seems to be critically dependent on body fat distribution. Individuals with greater degrees of central obesity are more prone to develop this syndrome compared to those with a peripheral body fat distribution [Kissebah and Krakower, 1994]. Accumulating evidence supports a strong correlation between human visceral adiposity, insulin resistance and the risk for cardiovascular disease [Zimmet *et al.* 2001] and experimental studies investigating the role of abdominal obesity in the pathophysiology of metabolic disease and cardiovascular risk suggest the portal theory of insulin resistance, in which free fatty acids (FFAs) from visceral fat directly enter the liver and have a detrimental effect on insulin action [Bergman *et al.* 2007]. Insulin resistance is believed to play a key role in the MetS, as evidenced by the fact that both hyperinsulinemia and insulin resistance are present in cases of obesity, hypertension, diabetes, and dyslipidemia. Accumulating evidence indicates that both insulin resistance and hyperinsulinemia may be causally related to hypertension [Sowers, 2004a], type 2 diabetes mellitus, and cardiovascular disease [Sowers and Frohlich, 2004]. Additionally, type 2 diabetes mellitus and hypertension are both associated with insulin resistance and accompanying hyperinsulinemia [Epstein and Sowers, 1992].

These observational data suggest an important role for factors predisposing for obesity and for insulin resistance in the pathogenesis of the MetS. Nevertheless, the question why some obese people develop the MetS and others don't remains so far unanswered. Our current understanding suggests obesity and insulin resistance as the two major metabolic factors leading to a clustering of metabolic risk factors, which clinically result in the diagnosis MetS depending on the adjustment of the presumed but so far unknown metabolic susceptibility factor.

The key role of obesity, adipose tissue and insulin resistance in the development of the MetS

Visceral Obesity and waist circumference
Central obesity and associated insulin resistance and hyperinsulinemia may contribute to

an increased risk of cardiovascular disease and stroke [Sowers, 2001]. The metabolic characteristics of fat tissue present in omental and paraintestinal areas promote insulin resistance and hyperinsulinemia [Banerji *et al.* 1997; McFarlane *et al.* 2001; Tchernof *et al.* 1996]. Relative to peripheral fat tissue, visceral or intra-abdominal fat is more resistant to the metabolic effects of insulin and more sensitive to the metabolic effects of the lipolytic hormones glucocorticoids and catecholamines [Banerji *et al.* 1997; Tchernof *et al.* 1996]. This mechanism results in an increased release of FFA into the portal system and provides increased substrate for the hepatic production of triglycerides and may impair the first-pass metabolism of insulin [Banerji *et al.* 1997; McFarlane *et al.* 2001].

Whereas visceral adipose tissue promotes a higher rate of flux of adipose tissue-derived FFA to the liver through the splanchnic circulation, abdominal subcutaneous fat is expected to release lipolysis products into the systemic circulation and avoid more direct effects on hepatic metabolism, for instance glucose production, lipid synthesis, and secretion of prothrombotic proteins such as fibrinogen and plasminogen activator inhibitor [Aubert *et al.* 2003]. The hyperinsulinemia associated with visceral obesity therefore may directly contribute to an increased risk of cardiovascular disease and stroke [Despres *et al.* 1996]. Visceral adipose tissue promotes the development of lipotoxicity in peripheral tissues by secreting adipocytokines [Lelliott and Vidal-Puig, 2004].

Despite these important differences between visceral and abdominal obesity, the clinical diagnosis of the MetS does not differentiate between the origins of body fat, which is a major point of criticism with respect to the practicability of the diagnosis 'MetS' for predicting cardiovascular disease. The definition of the 'MetS' includes waist circumference, which may sometimes be misleading. The relative predominance of visceral rather than subcutaneous adipose tissue with increasing waist circumference in Asians and Asian Indians renders the relative prevalence of the syndrome higher than in African-American men in whom subcutaneous fat predominates [Tanaka *et al.* 2003]. However, waist circumference is directly related to all-cause mortality when adjusted for body mass index (BMI) [Bigaard *et al.* 2005], highlighting the importance of visceral over subcutaneous fat deposits

and the incorporation of waist circumference measurement in the diagnosis MetS.

Despite the importance of obesity as a single component of the MetS, we should remember that patients of normal weight can also be insulin-resistant [Ruderman *et al.* 1998]. Especially evidence from the less common disorders does support a genetic basis of the syndrome including single gene defects e.g. in the peroxisome-proliferator activated receptor complex, lamin A/C, 1-acylglycerol-3-phosphate, O-acyltranferase, seipin [Hegele, 2003], the β_2-adrenergic receptor [Dallongeville *et al.* 2003] and adiponectin [Fumeron *et al.* 2004]. This suggests the existence of an independent factor causally determining the metabolic susceptibility.

The role of adipose tissue

The classical functions of adipose tissue are heat insulation, mechanical cushioning, and as a storage site for fat in the form of triglycerides. However, this view has been dramatically changed with the recognition of the adipose tissue as a key endocrine organ [Ronti *et al.* 2006]. Adipose tissue secretes active endocrine, paracrine and autocrine substances in response to different stimulus. Some of them are mainly released by the adipose tissue (e.g. leptin and adiponectin) while others are shared with other systems (e.g. TNFα) thus interweaving its function in systemic whole-organism regulations. Chronically inadequate energy balance may be a key factor, stressing the system. In this situation, an adipose tissue functional failure may result in changes in systemic energy delivery and impaired glucose consumption including changes in adipokines secretion and vascular effects [Laclaustra *et al.* 2007]. Whereas hopes attributed to the detection of leptin were premature, adiponectin seems to possess antiatherogenic and anti-inflammatory effects and may be protective against cardiovascular disease development [Smitko *et al.* 2007]. Except in a small number of people whose obesity is due to inherited leptin deficiency [Farooqi *et al.* 2002], attempts at using leptin therapeutically have not been effective. In contrast, adiponectin appears to serve as a protective adipocytokine, balancing the detrimental, proinflammatory actions of leptin and resistin. Obese subjects have a significantly lower level of plasma adiponectin when compared with nonobese subjects, and the adiponectin levels were negatively correlated to BMI in males and females [Arita *et al.* 1999].

Circulating adiponectin concentrations are correlated more negatively with visceral fat area than with subcutaneous adiposity, suggesting a physiological link with the MetS. Hypoadiponectinemia appears to place an individual at risk for the development of insulin resistance and progression towards diabetes. Lower concentrations of plasma adiponectin have been associated with both essential hypertension and dyslipidemia [Adamczak *et al.* 2003] and in patients with coronary artery disease, stroke and peripheral artery disease (for detailed review see Szmitko, 2007). Adiponectin appears to protect the vasculature as a molecule with anti-inflammatory properties and serves to protect against the onset of endothelial dysfunction [Motoshima *et al.* 2004].

Insulin resistance

Insulin resistance (IR) is one of the most accepted causes for the clinical development of the MetS. The presence of IR displays an impaired biologic response of target organs to insulin [Sowers *et al.* 1994]. As possible mechanisms, pre-receptor, receptor and post-receptor defects have been proposed as possible mechanisms (see Table 1 for pre- and post-receptor defects). Impaired signaling at the receptor level results in a cascade of events within the target tissue, eventually resulting in impaired glucose transport and a compensatory increase in insulin to overcome the resistance [Gill *et al.* 2005]. Several signaling pathway defects are implicated in insulin resistance. The most studied pathway involves the phosphatidylinositide 3-kinase (PI3-kinase) and protein kinase B (Akt) pathway. Insulin and insulin growth factor (IGF) act on the same receptor but use different intracellular signaling pathways [Sowers, 1997a].

Upon binding to their receptors, in the insulin sensitive state, there is autophosphorylation of the beta-subunit, which mediates the interaction between the receptor and cellular proteins [Gill *et al.* 2005]. Several proteins are then rapidly phosphorylated on tyrosine residues by ligand-bound insulin receptors, including insulin receptor substrate-1 (IRS-1). IRS docking proteins bind strongly to the enzyme PI3-kinase. Insulin and insulin growth factor-I-stimulation increases the amount of PI3-kinase associated with IRS, and the binding process is associated with increased activity of the enzyme [Sowers, 2004]. Activation of the enzyme is crucial for transducing the actions of these peptides in cardiovascular tissue as well as conventional insulin-sensitive tissues. The interruption of this signaling cascade results in a resistance to the actions of insulin with resultant hyperinsulinemia [Gill *et al.* 2005].

Numerous factors are associated with signaling defects: a key role is played by the adipocyte, which has been recognized as an endocrine tissue that secretes metabolically active factors [Schrauwen and Hesselink, 2004]. FFA contribute to impaired glucose tolerance by accumulation in nonadipose tissues [Schrauwen and Hesselink, 2004]. Intracellular accumulation of FFA results in overproduction of toxic metabolites that contribute to defective insulin signaling [Boden *et al.* 2002]. Adipocytokines such as adiponektin, resistin, leptin, TNFα, and IL-6 have been implicated to be associated with insulin resistance and consequent development of the MetS but further research is necessary to reveal the underlying pathophysiological mechanisms and pathways.

Table 1. Mechanisms of insulin-resistance.

Pre-Receptor Defects	Post-Receptor Defects
Decreased delivery of insulin and glucose to skeletal muscle due to: • Increased reactive oxygen species • Reduced generation of nitric oxide • Vascular rarefaction • Vascular hypertrophy • Increased vasoconstriction	Impaired signaling due to: • Decreased signaling through PI3K-Akt pathway • Decreased GLUT-4 content and translocation to the plasma membrane • Decreased glycogen synthase activity • Increased oxidative stress • Increased intramyocellular lipids • Altered skeletal muscle fiber type • Decreased insulin sensitive skeletal muscle fibers • Decreased mitochondrial content
adapted from: Gill *et al.* 1997	

Insulin resistance is also dependent on a number of genetic factors regulating the action of insulin at target organ level such as PC-1, which is a transmembrane glycoprotein that inhibits tyrosine kinase activity [Frittitta *et al.* 2001] and IRSs which is a key substrate for the insulin receptor and regulates insulin signaling in skeletal muscle, adipose tissue and the vasculature [Baroni *et al.* 2001].

Polycystic ovary syndrome

An example of a severe obesity-related cardiovascular complication affecting young women also supporting the endocrine genesis of cardiometabolic complications is the polycystic ovary syndrome (PCOS), a condition of ovarian dysfunction that affects 6 to 10% of women of reproductive age. The clinical symptoms are menstrual cycle irregularities, androgen excess and polycystic ovaries. Many women with PCOS are obese, and Ehrmann reported that about a third of US women with PCOS exhibit symptoms of the MetS, such as increased hyperglycemia, insulin resistance, and dyslipidemia [Ehrmann *et al.* 2006]. PCOS is also associated with increases in blood pressure (BP) attributed to increases in androgen levels. However, the mechanisms by which androgens might increase BP is unclear but a role for the renin-angiotensin-system (RAS) has been suggested in mediating androgen-stimulated increases in blood pressure. In women with PCOS, plasma renin activity was found to be elevated compared with a control group [Uncu *et al.* 2002]. Plasma prorenin has also been shown to be higher in women with PCOS and correlates positively with serum androgen levels [Morris *et al.* 1995]. However, there is also evidence for involvement of the endothelin (ET)-system in PCOS-associated hypertension: ET-1 has been found in human follicular fluid, and ET-1 mRNA expression has been found in ovarian tissues [Gentili *et al.* 2001]. Diamanti-Kandarakis *et al.* reported that serum endothelin levels were higher in women with PCOS independent of BMI, and that a positive correlation was found between free androgen index and plasma-ET-levels [Diamanti-Kandarakis *et al.* 2001]. Because angiotensin II has been shown to stimulate ET production, it is possible that androgens may directly stimulate endothelin or may stimulate the RAS to increase endothelin, thus leading to the expression of two powerful vasoconstrictors that could influence blood pressure in women with PCOS [Reckelhoff, 2007].

Hypertension, hyperlipidemia and atherosclerosis as concomitant diseases of obesity and insulin resistance

Hypertension

The relationship between insulin resistance and hypertension is well established [Ferrannini *et al.* 1987]. The fact that hypertensive patients have higher fasting and postprandial insulin levels independent of body mass index or body fat distribution suggests a direct correlation between blood pressure and plasma insulin levels [Shen *et al.* 1988]. It is still unclear by which mechanism insulin-resistance causes hypertension [Govindarajan *et al.* 2005]. However, it is well established that insulin itself has direct effects on the vasculature [Baron, 1996] and is a well known dilator in various vascular tissues *in vivo*, including vein [Morris *et al.* 1995] and brachial artery [Lembo *et al.* 1994; Tack *et al.* 1996]. It has been suggested that the vasodilatory effect of insulin might be impaired in an insulin-resistant condition [Tooke and Hannemann, 2000] which might contribute to increases in blood pressure. In addition, it has been experimentally shown that overall dyslipidemia could contribute to a chronic increase in vascular tone and, consequently, to hypertension [Banos *et al.* 1997]. The vasoreactivity is generally affected by a constrictive effect of fatty acids on blood vessels itself [Tripathy *et al.* 2003] which might also contribute to the development of hypertension. Therefore, based on the current understanding, insulin resistance and hypertension are causally related and the treatment of either results in the improvement of the other.

Increasing evidence suggests a specific pathophysiologic role for the RAS especially in patients with hypertension in accompaniment with the MetS [McFarlane *et al.* 2003]. Plasma renin activity (PRA) is a powerful cardiovascular risk factor independently of other known risk factors [Brunner *et al.* 1972] and clear associations between the RAS and metabolic cardiovascular risk factors have been shown [Allikmets *et al.* 1996; Egan *et al.* 1994; Goodfriend *et al.* 1995; Lind *et al.* 1992; Phillips *et al.* 1995] whereas no relationship between serum levels of aldosterone and cardiovascular risk seems to exist [Lind *et al.* 1998]. A clear relationship between high PRA-levels and hyperinsulinemia has been established in several studies [Allikmets *et al.* 1996; Egan *et al.* 1994; Goodfriend *et al.* 1995; Phillips *et al.* 1995] and Lind was able

to confirm also in untreated patients with essential hypertension that insulin resistance is related to elevated levels of PRA when evaluated by the euglycaemic hyperinsulinaemic clamp [Lind *et al.* 1998]. However, the mechanisms connecting high PRA and insulin resistance are as yet unknown. In contrast, a causal association of insulin resistance and compensatory hyperinsulinemia with blood pressure elevation is established. Mechanisms involved in this relationship include insulin-mediated sodium retention, stimulation of the sympathetic nervous system, and promotion of vascular cell's growth or impairment of endothelial nitric oxide (NO) production in insulin-resistant states [Sartori *et al.* 1999].

There is also accumulating evidence for an involvement of the endothelin system in the development of hyperinsulinemia induced hypertension [Sarafidis, 2007]. Endothelin-1, which is considered to be the most powerful natural constrictor is the main effector of the endothelin system and mediates its effects via ET-A and ET-B receptors in the vasculature. Although vasoconstriction is its predominant action, ET-1 can also act on ET-B receptors present in endothelial cells in an autocrine fashion and promote production of NO and vasodilating prostaglandins [Luscher and Barton, 2000]. Although the precise role of ET-1 in the development of systemic hypertension has not yet been fully elucidated, data from *in vitro*, animal, and human studies suggest that insulin both stimulates ET-1 production from endothelial cells and upregulates its actions in vascular smooth muscle cells [Piatti *et al.* 1996; Wolpert *et al.* 1993]. This suggests that increased ET-1 could play an important role in BP elevation and insulin-resistant states.

Hyperlipidemia

Atherogenic dyslipidemia is characterized by elevated triglycerides, low high-density lipoprotein cholesterol (HDL-C), increased small dense LDL particles, and normal to slightly elevated LDL-C [Ginsberg, 2003] although it is not completely clear if isolated triglyceride elevations bear an independent risk for atherosclerosis. Atherogenic dyslipidemia is generally regarded as an independent risk factor for cardiovascular events besides increased levels of total cholesterol, LDL-cholesterol and reduced levels of HDL-cholesterol [Fonseca, 2005]. The development of atherogenic dyslipidemia is mediated largely by the effect of circulatory free fatty acids

on the liver, stimulating synthesis of triglycerides and the secretion of very low density lipoprotein cholesterol (VLDL-C). Increased VLDL-C levels usually result in HDL-C reductions because cholesteryl ester transfer protein (CETP) transfers cholesterol from HDLs to LDLs. CETP-inhibitor therapy therefore results in increased HDL-levels [Brousseau *et al.* 2004]. Insulin has been reported to downregulate the activity of lipoprotein lipase which contributes to the breakdown of VLDL-C. Therefore, hyperinsulinemia increases the production and decreases the metabolism of VLDL-C.

There is still an unanswered question with respect to the suspected atherogenic role of elevated triglyceride levels. Hypertriglyceridemia, both in the MetS and in type 2 diabetes, results from increased plasma concentrations of VLDL, with or without chylomicronemia, deficient lipoprotein lipase activity, increased cholesteryl ester transfer protein activity and increased flux of FFA to the liver [Yuan *et al.* 2007]. Elevated triglyceride levels are often associated with non-alcoholic fatty liver disease in patients with obesity and insulin resistance [Clark, 2006] and have been shown to impair endothelium-dependent vasodilation in hypercholesterolemic patients without diabetes [Schneider *et al.* 2003] suggesting a role for triglycerides in the development of atherosclerosis. Triglyceride-rich lipoproteins and their remnants may directly contribute to the formation of arterial-wall foam cells. Chylomicrons are not directly atherogenic, although there are rare reports of atherosclerosis in patients with hyperchylomicronemia [Benlian *et al.* 1996] whereas chylomicron remnants, VLDL and intermediate-density lipoproteins are atherogenic [Zilversmit, 1979]. Whereas a strong independent relation between plasma triglyceride levels and the likelihood of cardiovascular disease have been suggested [Criqui *et al.* 1993], meta-analyses including thousands of patients followed up for more than 10 years showed that a triglyceride elevation of 1 mmol/l increased the risk of cardiovascular disease by 32% in men and 76% in women, independent of HDL-C levels [Hokanson and Austin, 1996]. However, in the recently published FIELD study, therapeutic triglyceride reduction with fenofibrate did not significantly reduce the risk of the primary outcome of coronary events [Keech *et al.* 2005]. Therefore, hypertriglyceridemia might be interpreted more as a symptom indicating supernutrition and a shift of the overall metabolic status

towards a condition which might rather develop into clinical manifestation of the MetS or remain a pure symptom of supernutrition. This development into the one or the other direction might be determined by a metabolic master switch determining the overall metabolic susceptibility.

Atherosclerosis

There is evidence supporting the view that the MetS predicts cardiovascular disease, but also evidence against this interpretation. Five studies investigating this issue [Hunt *et al.* 2004; Isomaa *et al.* 2001; Jeppesen *et al.* 2000; McNeill *et al.* 2005; Sattar *et al.* 2003] suggest a strong correlation between manifestation of the MetS and an increased risk for cardiovascular disease. In contrast, other epidemiologic studies suggest that the individual components of the MetS predict the outcomes well enough and that the risk associated with the MetS is not greater than the sum of its parts [Bruno et el. 2004; Resnick *et al.* 2003; Wilson *et al.* 1998]. These differences in outcomes might be explained by the presence or absence of inflammatory processes which play a fundamental role in the initiation, propagation, and complications of atherosclerosis. Key events in the inflammatory process include the increased expression of leukocyte adhesion molecules such as vascular cell adhesion molecule-1 by endothelial cells, the expression of growth factors, the release of chemoattractants within atheromata, and the elaboration of inflammatory cytokines (e.g. interferon γ and tumor necrosis factor α) [Libby and Plutzky, 2007]. Inflammation accompanies or precedes the metabolic syndrome and seems to play an important role in the development of atherosclerosis [Lau *et al.* 2005]. From a pathophysiological point of view, studies in experimental models of obesity have shown that the accumulation of fats in mice leads to a damaging secretion of cytokines by fat tissue with a subsequent reduction in insulin sensitivity [Klover *et al.* 2003]. Epidemiological studies have clearly confirmed that inflammatory markers, for instance CRP, increase with the presence of different components of the metabolic syndrome [Festa *et al.* 2000]. More interestingly, a strict control of diabetes has recently been shown to be associated with favourable changes in CRP levels only in the absence of excessive weight gain [Schaumberg *et al.* 2005]. Taking together this line of evidence it becomes clear that inflammation precedes and accompanies the metabolic syndrome and atherosclerosis. Regarding the MetS as an endocrine disease, the question arises what the

triggering factor for the development of a general proinflammatory state might be. However, no clear answer can be given yet.

Pharmacotherapeutic strategies targeting the MetS

ACE-inhibitors (ACE-I) and AT$_1$-receptor antagonists (ARBs)

Hypertensive patients are prone to insulin resistance and there is widespread agreement that the RAS plays a pivotal role in the pathogenesis of cardiovascular disease and insulin resistance by inhibiting the actions of insulin in vascular and skeletal muscle tissue [Sowers, 2004]. Insulin resistance is known to activate the RAS [DeFronzo and Ferrannini, 1991]. Angiotensin II as the main effector of the RAS not only increases the vascular resistance, but also increases hepatic glucose production and decreases insulin sensitivity. Therefore it is obvious that pharmacological inhibition of the RAS does not only exert antihypertensive effects but also targets insulin resistance and improves the glucose metabolism. An improvement in insulin sensitivity has been reported by adding an ACE-I to a tissue culture system suggesting therapeutic effects independent of the microcirculation. This improvement in insulin sensitivity at a cellular level is indicated by an increase in glucose transporter-4 protein and activity of hexokinase, which is a key enzyme in glucose metabolism in the skeletal muscle of obese rats treated with an ACE-I [Jacob *et al.* 1996]. The mechanisms are not completely understood but it has been suggested that interruption of the tissue RAS may improve insulin signalling by abrogating the inhibitory effects of Angiotensin II on phosphatidyl inositol-3 kinase and protein kinase B signalling [Folli *et al.* 1997; Nawano *et al.* 1999; Velloso *et al.* 1996]. Angiotensin II, acting via an angiotensin II type 1 G protein linked receptor, interferes with the signalling of insulin and insulin-like growth factor through the phosphatidyl inositol-3 kinase and protein kinase B signalling pathways, but it does not affect the synergistic action of insulin and insulin-like growth factor with angiotensin II and with growth factors that promote left ventricular hypertrophy and vascular growth and remodelling [McFarlane *et al.* 2001; Sowers *et al.*. 2001]. ACE-I and ARBs inhibit these unfavourable effects of Angiotensin II and thereby improve metabolic and vascular functions besides their well documented antihypertensive efficacy. Therefore, an increasing number

of experts support ACE-I as first line therapy in the MetS, especially when type 2 diabetes or renal disease is present [Chobanian *et al.* 2003; Deedwania and Fonseca, 2005].

The question whether an ACE-I or an angiotensin receptor blocker (ARB) should be used remains controversial. There is consensus that ARBs may be used when ACE-I are not tolerated and have similar beneficial effects in preventing diabetes [Barnett *et al.* 2004]. In contrast to ACE-I, ARBs directly block the AT_1-receptor and hence also the action of angiotensin II produced via non-ACE-dependent pathways. However, there are two additional pharmacological arguments supporting the use of an ARB. Considering the pharmacological differences between ACE-I and ARBs it has to be pointed out that treatment with an ARB results in significant increases of the pleiotropic and vasodilatory angiotensin II – metabolite angiotensin 1-7 [Ang-(1-7)] [Schindler *et al.* 2007], which might improve the antihypertensive effects, whereas treatment with an ACE-I results in increases of bradykinin-levels, which do not seem to have beneficial vascular effects [Schindler *et al.* 2007]. The second consideration supporting the use of a specific ARB targets the energy metabolism: Recently, the ARB telmisartan was found to act as a partial agonist of the peroxisome proliferator-activated receptor γ (PPAR γ), thus reducing glucose, insulin, and triglyceride levels in an experimental model [Schupp *et al.* 2004]. PPAR γ influences the gene expression involved in carbohydrate and lipid metabolism, and pioglitazone and rosiglitazone, which are ligands for PPAR γ, improve insulin resistance in diabetic patients [Marx *et al.* 2004]. PPAR γ-agonists also exert anti-inflammatory, anti-oxidative and anti-proliferative effects on vascular wall cells, thus decreasing the risk for atherosclerosis [Marx *et al.* 2004]. These observations suggest telmisartan as a promising cardiometabolic ARB, which targets the RAS via selective AT_1-receptor antagonism and insulin resistance via binding to the intracellular PPAR γ-complex, which has been shown to improve insulin resistance.

It has been recently suggested that drugs targeting the RAS might also be a beneficial therapeutic strategy for the treatment of obesity-related hypertension [Sharma, 2004]. Excess weight gain is associated with increased renal sympathetic activity, resulting in sodium retention [Morgan *et al.* 1995]. Increased sympathetic activity in turn stimulates renin release which contributes to increased blood pressure. Angiotensin II as a RAS-effector seems to be involved in the control of adiposity by regulating lipid synthesis and storage in adipocytes [Sharma *et al.* 2002]. This regulation may be mediated through insulin-response sequences in a glucose dependent manner [Kim *et al.* 2001].

Endothelin (ET)-Antagonists

In vitro studies have repeatedly shown that insulin promotes ET-1 production from endothelial cells as well as ET-1-actions in VSMCs. *In vivo*, euglycemic hyperinsulinemia increases circulating ET-1 in healthy individuals and in subjects with various conditions associated with IR, a finding which is consistent with elevated ET-1 levels in insulin-resistant states [Sarafidis and Bakris, 2007]. Therefore, therapy with a selective or unselective endothelin-antagonist might improve hypertension and insulin-resistance. However, the study evidence in humans is still very limited. There is so far evidence in favour of a possible contribution of increased ET-1 activity in abnormal vascular function and hypertension in insulin-resistant states. Cardillo *et al.* have shown that selective ET-A-blockade in the forearm resulted in a significant increase in forearm blood flow (FBF) in patients with type II diabetes but not in healthy individuals, whereas nonselective ET-A/ET-B blockade in diabetics did not significantly modify the effects of ET-A antagonism [Cardillo *et al.* 2002a]. In another study, unselective ET-blockade produced a significant increase in FBF from baseline and a significant potentiation of endothelium-dependent vasodilation in hypertensive patients but not in controls [Cardillo *et al.* 2002b]. Considering a potential role for endothelin in hypertension and in insulin-resistant states especially with respect to the ability of angiotensin II to stimulate ET production, endothelin-antagonists might be an additional therapeutic option for treating the MetS, maybe in combination with a drug inhibiting the RAS. However, ET-antagonists are currently clinically used only for the indication pulmonary hypertension. Therefore, randomized controlled clinical trials in patients are definitely needed before the clinical relevance of endothelin-blockade for the pathogenesis of the MetS can be finally judged.

Calcium channel blockers (CCBs)

CCBs appear to have beneficial effects with respect to maintenance of renal blood flow and glomerular filtration rate [Sowers, 1997b].

The main advantage for using CCBs as antihypertensive drugs in the MetS is that the metabolic abnormalities associated with diuretic and β-blocker antihypertensive therapy, such as hypokalemia, hypercalcemia, hyperuricemia, unfavourable lipid changes, and hyperglycemia are generally not observed with calcium antagonists.

PPAR-receptor complex stimulation as therapeutical target

PPARs are ligand-activated transcription factors and belong to the nuclear receptor superfamily, which also includes the steroid and thyroid hormone receptors. The PPAR family consists of three members, α, γ and β/δ, which share $\sim$ 60 to 80% homology in their ligand- and DNA-binding domains. Although there are no proven pathways for endogenous ligands *in vivo*, all PPARs are activated by FFAs.

PPARα can be activated by certain polyunsaturated fatty acids, by oxidized phospholipids and by lipoprotein lipolytic products [Ziouzenkova *et al.* 2003]. Fibrates and gemfibrocil are synthetic ligands [Formann *et al.* 1997], which are used as drugs for the treatment of hypertriglyceridemia [Yuan *et al.* 2007]. PPARα regulates genes that are involved in lipid and lipoprotein metabolism. PPARγ is activated by prostaglandin-derivatives and forms of oxidized linoleic acid as natural ligands. Although these endogenous ligands can activate PPARγ *in vitro*, there are currently no proven pathways *in vivo*. Synthetic ligands currently available for drug treatment include the thiazolidinediones (glitazones) rosiglitazone and pioglitazone. Troglitazone had to be dropped from the market due to serious liver toxicity. Stimulation of PPARδ stimulates fatty acid oxidation primarily in muscle but also in adipose tissue. PPARδ enhances fatty acid catabolism and energy uncoupling in adipose tissue and muscle, and it suppresses macrophage-derived inflammation. Its combined activities in these and other tissues make it a multifaceted therapeutic target for the metabolic syndrome with the potential to control weight gain, enhance physical endurance, improve insulin sensitivity, and ameliorate atherosclerosis [Barish *et al.* 2006]. Reduced atherogenesis has been proposed in animal models as main effect of PPARδ-agonism. An inflammatory switch model has been suggested predicting that PPARδ ligands, as with genetic deletion of PPARδ, should ameliorate inflammation [Lee *et al.* 2003].

These aggregate effects suggest that high-affinity PPARδ synthetic drugs may uniquely target multiple components of the metabolic syndrome, including obesity, insulin resistance, hyperglycemia, dyslipidemia and atherosclerosis. To date, the influence of systemic administered PPARδ activators on atherosclerosis has not been reported and data from clinical studies using a PPARδ-agonist are still lacking. From a theoretical standpoint, PPARδ-agonists might become very effective instruments to treat the MetS because it targets multiple organs (Table 2). Although safety concerns about PPARδ-targeted compounds have been raised, further studies in patients to define the potential of these drugs to treat the MetS are definitely needed because the therapeutic benefit might overbalance the risk. Figure 1 gives an overview about different therapeutic effects of different PPAR-agonists on target organs in patients with the MetS.

Fibrates and namely feno- and bezafibrate are used clinically for the treatment of hypertriglyceridemia. In the liver, activation of PPARα induces the expression of the fatty acid transport protein and fatty acid translocase which facilitates the transport of FFAs across the cell membrane. PPARα-activation also directly increases the transcription of enzymes of the peroxisomal β-oxidation pathway and *de novo* fatty acid synthesis by blocking enzymes like acetyl-CoA carboxylase and fatty acid synthase [Keating, 2007]. Therefore, PPARα functions as a fatty acid sensor and important regulator of fatty acid metabolism and energy homeostasis. However, with respect to the treatment of the MetS, PPARα-stimulation with fenofibrate or bezafibrate should not be the first therapeutic option because the effects of fibrates on insulin sensitivity in humans have not been extensively investigated. As already discussed above, the FIELD study did not show a significantly reduction in the risk of the primary outcome of coronary events which at least questions the therapeutic benefit of drug therapy with fibrates in patients with the MetS [Keech *et al.* 2005].

Glitazones functioning as PPARγ-activators play an important role in glucose homeostasis and reduce peripheral insulin resistance of patients with type 2 diabetes [Saltiel and Olefsky, 1996]. PPARγ is expressed at high levels in adipose tissue and is a central regulator of adipocyte gene expression and differentiation. The mechanisms underlying insulin-sensitizing

Table 2. Therapeutic targets of PPARδ in the metabolic syndrome.

Organ	Target	Function
Heart	Increased contractile function	• Increased fatty acid transport and oxidation
Muscle	Increased endurance capacity	• increased fatty acid transport and oxidation
		• increased thermogenesis
		• increased slow-twitch fibers
Adipose tissue	Prevention of obesity	• increased fatty acid transport and oxidation
		• increased thermogenesis
Artery	Improvement of Lipid profile	• Increased HDL-cholesterol
Liver	Decreased glucose output	• Increased pentose phosphate shunt
Macrophage	Antiinflammatory switch	• Binding/release of BCL-6
adapted from Barish *et al.* 2006.		
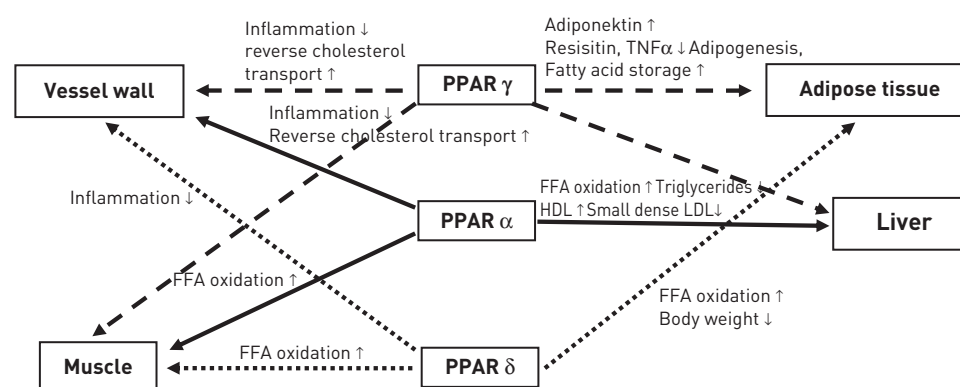
Figure 1. Therapeutic effects of different PPAR-agonists on target organs in patients with MetS (adapted from Blaschke *et al.* 2006).

effects of TZDs are complex and not completely understood. Expression of resistin and TNFα, which both induce insulin resistance, are reduced by PPARγ-ligands, suggesting that the insulin-sensitizing effect of PPARγ-agonists is related to their anti-inflammatory properties [Marx *et al.* 2003; Steppan *et al.* 2001]. Table 3 displays the available study evidence for anti-inflammatory effects of PPARγ-agonists *in vitro*, *in vivo* and in patients. A large body of evidence also shows that PPARγ seems to be a master regulator in the formation of fat cells and their ability to function normally in the adult [Rosen *et al.* 2000]. PPARγ is induced during adipocyte differentiation, and forced expression of PPARγ in non-adipogenic cells effectively converts them into mature adipocytes. Therefore, the adipose tissue might be directly involved in the development of increased metabolic susceptibility predisposing for the clinical development of the MetS in presence of an inflammatory stimulus. But how

does pharmacological PPARγ – activation in the adipocyte results in a systemic improvement in insulin sensitivity in liver and muscle? Two plausible mechanisms have been recently suggested by Evans *et al.* [2004]: First, PPARγ-activation might improve the ability of adipose tissue to store lipids, thereby reducing lipotoxicity in muscle and liver. This results in body-wide lipid-repartitioning by increasing the triglyceride content of adipose tissue and lowering FFAs and triglycerides in the circulation, liver and muscle, thereby improving insulin sensitivity. Second, PPARγ-specific drugs alter the release of signaling molecules from fat, including leptin, TNFα, resistin and adiponectin, which have far-reaching metabolic effects in other tissues, thereby improving the general metabolic susceptibility. The fact that glitazones and especially pioglitazone has been shown to be effective in the treatment of patients with non-alcoholic steatohepatitis provides further evidence for the

Table 3. Anti-inflammatory effects of PPARγ-agonists.

in vitro	*in vivo* (animal)	*in vivo* (patients)
• Reduction of superoxide generation [Mehta *et al.* 2003] • In endothelial cells: Inhibition of expression of vascular cell adhesion molecule-1, intercellular cell adhesion molecule-1 and lectin-like oxidized LDL-receptor-1 [Metha *et al.* 2003; Pasceri *et al.* 2000] • Inhibition of vascular smooth muscle cell migration, proliferation, and matrix metalloproteinase-9 expression [de Dios *et al.* 2003; Law *et al.* 2000; Marx *et al.* 1998] • Reduction of production of inflammatory cytokines (e.g. TNFα, IL-6, IL-1β [Jiang *et al.* 1998]), inducible NO-synthase, matrix metalloproteinase-9 [Marx *et al.* 1998], and scavenger receptor-A in monocytes/macrophages [Ricote *et al.* 1998]	• Reduction of atherosclerotic lesions, including reduction of the recruitment of monocytes and macrophages to atherosclerotic lesions [Li *et al.* 2000; Marx *et al.* 2004; Pasceri *et al.* 2000]	Reduction of serum levels of CRP, IL-6, monocyte chemoattractant protein-1, PAI-1, soluble CD40 ligand and metalloproteinases-9 [Agarwal *et al.* 2006; Aljada *et al.* 2001; Haffner *et al.* 2002; Marx *et al.* 2003; Mohanty *et al.* 2004; Wang *et al.* 2005] • Reduction of the generation of reactive oxygen species by circulating polymorphonuclear and mononuclear cells [Aljada *et al.* 2001] • Reduction of NF-ΚB binding in circulating mononuclear cells [Aliada *et al.* 2001; Mohanty *et al.* 2005]

benefical metabolic effect of PPARγ-agonists [Lutchman *et al.* 2007]. These characteristics and especially the metabolic effects combined with anti-inflammatory effects suggest glitazones as promising therapeutic agents for the treatment of the MetS and should be systematically investigated in randomized controlled endpoint studies for this indication.

PPARα/γ dual agonists such as muraglitazar or tesaglitazar have been developed to target both PPARα and PPARγ simultaneously in order to produce synergistic antidiabetic and cardioprotective effects. Dual agonists have been demonstrated to reduce triglycerides, raise cardioprotective HDL levels and consequently improve insulin sensitivity [Kendall *et al.* 2006]. Unfortunately, developments of the PPARα/γ dual antagonists such as muraglitazar and tesaglitazar had to be terminated because of their side effects and serious safety concerns [Balakumar *et al.* 2007]. The side effects of these agents may be due to their imbalanced and maybe supra-therapeutic activity on PPARγ and α with desired therapeutic effects but also some of adverse events which are difficult to predict based on the expected pharmacological profile of the drug.

Statins
The pleiotropic effects of statins improves cardiovascular outcomes beyond their ability to improve atherogenic lipid profiles [McFarlane *et al.* 2002]. Modulation of endothelial function, plaque stabilization, attenuated atherogenesis, anti-inflammatory and antithrombotic effects might support the cardiometabolic risk reduction in patients with the MetS. However, beyond lipid-modifying and pleiotropic effects, effects of statins on glucose metabolism have also been proposed. The WOSCOPS study examining the development of new diabetes mellitus revealed that pravastatin therapy reduced the risk of developing diabetes by 30%, which was attributed to a reduction in triglycerides [Freeman *et al.* 2001]. As a potential underlying mechanism, statins may affect substrate delivery to insulin-sensitive tissues or modulate insulin-activated signalling cascades that mediate glucose uptake. Insulin increases skeletal muscle perfusion and substrate delivery by enhancing eNOS activity. Statins also increase eNOS expression, which may result in increased capillary recruitment and glucose disposal [Le Roith and Zick, 2001]. Therefore, statins might be a useful therapeutic option for the treatment of the MetS. However, as statins are primarily targeting more hyperlipidemia and

especially an atherogenic lipid profile as one symptom out of a cluster of syndroms, they should probably not be the first therapeutic option in MetS patients without severe lipid abnormalities.

CETP-inhibition with torcetrapib
CETP-inhibition has been regarded as a promising therapeutic concept to reduce the total cardiovascular risk. However, the CETP-inhibitor drug torcetrapib, which was designed to selectively increase HDL-levels by blocking CETP showed that, although the drug raises HDL as expected, it doesn't halt the progression of atherosclerosis. In two studies reported, combined therapy with atorvastatin and torcetrapib showed more than a 50% increase in HDL cholesterol and a 20% decrease in LDL cholesterol. However, both trials were stopped because of reported increased mortality. In addition, increased (BP) has been reported in both studies. These results suggest that the current understanding of good and bad lipoproteins might probably be too simplistic and probably it might be not only important to raise HDL but it might depend on how to raise HDL [Opar, 2007]. The clinical experience with torcetrapib demonstrated nicely that pure so-called lipid cosmetics without targeting the pathogenesis of the disease is not always suited to reduce cardiovascular morbidity and mortality. In addition, the experience with torcetrapib suggests that lipid abnormalities might be rather a symptom of the cluster than a cause for the clinical manifestation of the MetS and increased cardiovascular mortality. With respect to drug treatment for the MetS this might suggest that the therapeutic concept of PPARγ-stimulation might better target the pathogenesis of the MetS in order to be successful.

Sibutramine, orlistat and rimonabant
Sibutramine, a centrally acting appetite suppressant, and orlistat, a locally acting inhibitor of nutrient absorption, pharmacologically target obesity as a component of the MetS. Sibutramine acts on the CNS by inhibiting the reuptake of norepinephrine and serotonin and thereby amplifies satiety signals that induce a sensation of fullness. The STORM-trial (Sibutramine Trial of Obesity Reduction and Maintenance) demonstrated not only a significant weight loss but also an improvement of characteristics covered by the diagnosis of the MetS

such as triglycerides, HDL-cholesterol, waist circumference and insulin [James *et al.* 2000]. In this study, the favourable effect on metabolic syndrome components were regarded as the major benefit of sibutramine [Aronne *et al.* 2007].

Orlistat is a drug that reduces fat absorption by binding to pancreatic lipases, which partially inhibits the hydrolysis of triglycerides into absorbable free fatty acids and monoacylglycerols [Yanovski *et al.* 2002]. A European [Sjostrom *et al.* 1998] and a US [Davidson *et al.* 1999] multicenter study showed that patients treated with orlistat three times daily lost 10% of their initial body weight compared with a 6% weight loss in the placebo group. Orlistat helped patients to lose weight and switching study patients from treatment to placebo resulted in recurrent weight gain. Although orlistat has also been discussed to be more a lifestyle drug [Lexchin, 2001] there is study evidence that the drug might help to improve the overall cardiometabolic risk status in patients who are unable to lose weight on a diet.

Rimonabant is a selective cannabinoid-1 receptor blocker. The endocannabinoid system plays a role in the central and peripheral regulation of body weight and energy balance [Van Gaal *et al.* 2005]. Three Rimonabant In Obesity/Overweight (RIO)-trials demonstrated that the drug reduces weight and waist circumference and improves numerous cardiovascular and metabolic risk factors. In all trials, rimonabant was associated with an increased HDL cholesterol and decreased waist circumference and triglycerides [Despres *et al.* 2005; Pi-Sunyer *et al.* 2006; Scheen *et al.* 2006; Van Gaal *et al.* 2005]. Rimonabant acts through a unique mechanism to exert its effects on cardiometabolic risk independent of weight loss alone. Therefore, modulating the activity of the endocannabinoid system holds promise as an approach to treating obesity, dyslipidemia and atherogenesis, which are associated with the MetS.

However, sibutramine, orlistat and rimonabant are effective in supporting patients to lose weight and to reduce their cardiovascular risk profile but they do not causally target the pathogenesis of the MetS.

Conclusions
The identification of the underlying pathogenesis of the MetS is closely related with a successful

therapeutic strategy and optimal clinical management. The search for an endocrine 'master switch' determining the metabolic susceptibility and underlying the clinical manifestation of the MetS is still ongoing. There is considerable evidence supporting an interpretation of the MetS as an endocrine disease and RAS activation, obesity and insulin resistance seem to be mainly related to the pathogenesis of the MetS, whereas lipid abnormalities, hypertension and atherosclerosis might be rather comorbidities. Currently, PPARγ-stimulation with a thiazolidinedione is the only available strategy for targeting the MetS on a molecular basis although clinical study evidence is still limited. The most interesting pharmacological approach for causally targeting the MetS in the near future might be PPARδ-stimulation because this treatment principle has been suggested to uniquely target multiple components of the metabolic syndrome, including obesity, insulin resistance, hyperglycemia, dyslipidemia and atherosclerosis. Drugs providing PPARδ-stimulation and simultaneously exerting RAS-inhibitory properties might be especially promising therapeutic agents.

Conflict of interest
None declared.

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